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A MARKOV MODEL OF THE REPAIR-MISREPAIR PROCESS OF CELL SURVIVAL

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ABSTRACT

The repair-misrepair model of cell survival is formulated mathematically as a Markov process. The nucleus of a cell is described by the status of the lesions that resulted from exposure to radiation. At any time each of these lesions is either unrepaired, misrepaired, or eurepaired. A system of coupled differential equations for the probabilities of zero, one, two, ... unrepaired lesions is derived. The probability of survival of a cell is the probability of zero unrepaired or misrepaired lesions. Solutions for the probability of survival are obtained for four cases: three for lesions associated with the tracks of ionizing particles through the nucleus and one for lesions resulting from X rays and not distributed along tracks. These solutions reduce to simple forms for various limiting cases of the parameters. These limiting solutions bound the range of the probability of survival.

It is shown that when the average number of initial lesions per track is varied while the average number of lesions for the nucleus as a whole is held constant, the cells with a higher number of lesions per track (corresponding to higher LET) have a higher probability of survival than those with a lower number. This shows the effect of larger bunches of lesions on fewer tracks. It is known experimentally that when dose is held constant, a higher probability of survival corresponds to lower LET. These contrasting properties imply that the number of lesions per track must increase much less slowly with LET than in direct proportion, and may provide a means of testing the model.

I. INTRODUCTION

"The Repair-Misrepair Model of Cell Survival" by Tobias, Blakely, Ngo, and Yang describes the process by which lesions in the nucleus of a cell, produced as a result of exposure to ionizing radiation, are either repaired or misrepaired by enzymatic mechanisms.* This model of repair can be formulated mathematically as a Markov process. In such a formulation a single cell is described by the probabilities that it will evolve at random times through various states of partial repair. The initial state for this probability process is the one that exists after the exposure to radiation but before the enzymatic repair mechanisms have had an effect. This state is described by an initial probability distribution for the number and location of lesions within a single nucleus.

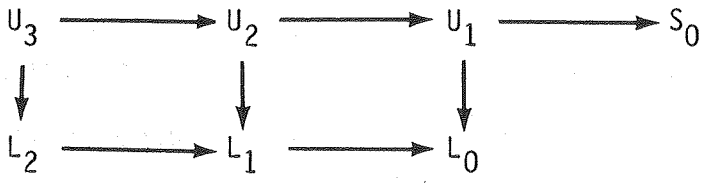
Two types of repair processes are considered: a linear process (self-repair) that involves only one lesion, and a quadratic repair process (cross-repair) that involves the interaction between a pair of lesions. A fraction ϕ of linear repairs are eurepairs and a fraction $1 - \phi$ are misrepairs. Similarly, a fraction δ of quadratic repairs are eurepairs and a fraction $1 - \delta$ are misrepairs.

At any time during the evolution of the nucleus, the possible states of the nucleus can be described by the number and location of unrepaired lesions and the number and location of eurepaired and misrepaired lesions. These states can be divided into three categories: survival states in which all the original lesions have been eurepaired, lethal states in which one or more

* Radiation Biology and Cancer Research, (A. Meyn and R. Withers, eds.) pp. 195-230. New York, Raven Press, 1980.

misrepairs have occurred, and uncommitted states in which all lesions have not been repaired but no misrepairs have yet occurred.

Initially, the nucleus is in an uncommitted state, and from there can evolve to another uncommitted state, a survival state, or a lethal state. Once the nucleus reaches a survival state it does not evolve further. From a lethal state the nucleus can evolve only to another lethal state. Let U_n and L_n denote respectively the uncommitted and lethal states with n lesions, and let S_0 denote the survival state. Then the possible steps in the evolution of a nucleus through three, two, one, and no lesions can be represented in a diagram as:



The goal of the Markov formulation is a mathematical model of this evolutionary process and the calculation of the probability $P_s(t)$ that the nucleus has evolved to a survival state at time t.

II. FORMULATION OF THE MARKOV MODEL

Lesions are produced near the track of an ionizing particle through a nucleus. On the other hand, X rays produce lesions whose locations in the nucleus are not correlated with each other. In this section a Markov model will be formulated for the case of ionizing particles; the case of X rays will be treated in the next section.

The Initial State

Let m denote the number of tracks through a particular nucleus; the value of m will vary from nucleus to nucleus. Let W denote the average value of m for all the nuclei; W is proportional to the dose D of radiation. The number m has a Poisson distribution with mean W, which shall be denoted by $P_p(m;W)$:

$$P_p(m;W) = \frac{1}{m!} (W)^m e^{-W}$$

Let k_i be the initial number of lesions along the ith track through a particular nucleus, and let V be the average number of lesions per track for all nuclei and tracks. Then k_i has a probability distribution $P_o(k_i)$ that depends on the shape and dimensions of the nucleus, the LET of the particles, and possibly other factors, but is independent of the dose of the radiation and of the number of lesions on the other tracks. $P_o(k_i)$ is a Poisson distribution for one simple case, a nucleus with uniform thickness parallel to the beam of particles.

The initial state of the nucleus is described by the number of lesions on each of the m tracks: $k_1, k_2, \ldots k_m$.

Subsequent States

Let n_i denote the number of unrepaired lesions remaining on the ith track at time t, and let x denote the number of misrepairs that have occurred. The state of the nucleus at time t is adequately described by:

$n_1, n_2, \ldots n_m, x.$

Three kinds of repairs can occur: self-repair, cross-repair between two lesions on the same track, and cross-repair between two lesions on different tracks. Each of these repairs corresponds to a different change in the state of the nucleus. A self-repair on track i is a transition between the states:

$$(n_1 \ldots n_i \ldots x) \rightarrow (n_1 \ldots n_i-1 \ldots x')$$

where $x' = x$ for eurepair and $x' = x + 1$ for misrepair. A cross-repair on track i is a transition between the states:

$$(n_1 \ldots n_i \ldots x) \rightarrow (n_1 \ldots n_i-2 \ldots x')$$

where n_i changes by two since two lesions are repaired in one cross-repair. A cross-repair between lesions on tracks i and j is a transition between the states:

$$(n_1 \ldots n_i \ldots n_j \ldots x) \rightarrow (n_1 \ldots n_i-1 \ldots n_j-1 \ldots x') \quad .$$

Transition Rates

For any time interval $(t, t + \Delta t)$ there exist probabilities for self-repair and cross-repair of the various lesions. If the nucleus is in a state j, then we assume the probability that it will evolve to a state k in the time interval Δt depends only on these states and not on the past history that led to the nucleus being in state j at time t. The transition rate is defined in terms of the probability $P_{jk}(\Delta t)$ that the nucleus will evolve from state j to state k in the interval Δt. The transition rate is:

$$c_{jk} = \lim_{\Delta t \to 0} \frac{P_{jk}(\Delta t)}{\Delta t}$$

The transition rate c_{jk} is an average value for all possible locations of the lesions along the tracks and for all possible locations of the tracks within the nucleus. It is also assumed that the probability of two repairs in the interval Δt, divided by Δt, goes to zero as $\Delta t \to 0$. Thus, the only non-zero transition rates are for the three transitions previously described, each of which involves only a single repair. Finally, it is assumed that these transition rates are independent of time.

Let λ denote the transition rate for the self-repair of one lesion, let κ^* denote the transition rate for the cross-repair of one pair of lesions on the same track, and let μ^* denote the transition rate for the cross-repair of one pair of lesions on one pair of tracks. Since there are n_i lesions on track i, the transition rate for self-repairs on track i is λn_i. Since the number of distinct pairs of lesions on track i is $n_i(n_i-1)/2$, the transition rate for cross-repair on track i is $\kappa^* n_i(n_i-1)/2$. Finally, since the number of pairs of lesions on tracks i and j is $n_i n_j$, the transition rate for cross-repair between tracks i and j is $\mu^* n_i n_j$. Let $\kappa = \kappa^*/2$ and $\mu = \mu^*/2$, then the total transition rates for all tracks for self-repair, intra, and between-track cross-repairs are:

$$\lambda \sum_i n_i$$

$$\kappa \sum_i n_i(n_i-1)$$

and

$$\mu \sum_i \sum_{j \neq i} n_i n_j$$

respectively. The last rate can be expressed alternatively as:

$$\mu \sum_i \sum_j n_i n_j - \mu \sum_i n_i^2$$

Note that the transition rates defined here depend on the actual number of lesions in a particular nucleus and not on the average number of lesions for all nuclei.

The transition rates κ and μ are products of two factors: an enzymatic repair rate and a probability that the two lesions are close enough to interact during the repair. This probability is larger for two lesions on the same track than for lesions on different tracks, that is, lesions on the same track are closer together on the average. Therefore, the transition rate for cross repairs on the same track should be greater than that for cross repairs on different tracks, that is, $\kappa \geq \mu \geq 0$. Define θ to be the ratio μ/κ, then θ must lie in the range $0 \leq \theta \leq 1$. The limiting case, $\kappa = \mu$, means that two lesions anywhere in the nucleus are as likely to interact as if they were on the same track. The other limit, $\mu = 0$, means that the maximum distance for interaction is so small that lesions on different tracks have effectively zero probability of interacting.

The Basic System of Differential Equations

The nucleus initially has no misrepairs. In order to reach a survival state, the nucleus must evolve only through states with no misrepairs. The probability of evolving through these states is described by a system of coupled differential equations. These equations follow from the three transition rates previously defined and the fractions ϕ and δ of linear and quadratic repairs that are eurepair. Let $P(n_1, n_2 \ldots n_m, t|m)$ denote the probability that at time t the nucleus is in the state $(n_1, n_2 \ldots n_m, x)$ with $x = 0$, given that there are m tracks through the nucleus. Let $\dot{P}$ denote $\partial P/\partial t$, then:

$$\dot{P}(n_1 \ldots n_m, t|m) = \phi\lambda \sum_i (n_i+1)\, P(n_1 \ldots n_i+1 \ldots n_m, t|m)$$

$$+ \delta\kappa \sum_i (n_i+2)(n_i+1)\, P(n_1 \ldots n_i+2 \ldots n_m, t|m)$$

$$+ \delta\mu \sum_i \sum_{j\neq i} (n_i+1)(n_j+1)\, P(n_1 \ldots n_i+1 \ldots n_j+1 \ldots n_m, t|m)$$

$$- [\lambda \sum_i n_i + \kappa \sum_i n_i(n_i-1) + \mu \sum_i \sum_{j\neq i} n_i n_j]\, P(n_1 \ldots n_m, t|m)$$

There is one such differential equation for the probability of each state, that is, for each set of numbers n_1, n_2 ... n_m. The first term on the right hand side represents transitions into the state n_1 ... n_i ... n_m, 0 by self-repair from the state n_1 ... n_i+1 ... n_m, 0. The second term represents transitions into the state n_1 ... n_i ... n_m, 0 by intratrack cross repair from the state n_1 ... n_i+2 ... n_m, 0. The third term represents transitions into the state n_1 ... n_i ... n_j ... n_m, 0 between-track cross repair from the state n_i ... n_i+1 ... n_j+1 ... n_m, 0. The fourth term represents transitions out of the state n_1 ... n_i ... n_m, 0 by self-repair and intratrack and between-track cross repairs.

The differential equation couples the probabilities of numerous states. The first term on the right hand side involves m states, the second term involves m more states, the third term involves $m(m-1)/2$ other states, and the left hand side and the fourth term on the right hand side involve only one state. For the case that all cross repair is misrepair, $\delta = 0$, the second and third terms on the right hand side drop out, which greatly simplifies the system of equations.

Since the initial number of lesions on one track is independent of the numbers on the other tracks, the initial probability $P(n_1 \ldots n_m, t|m)$ with $t = 0$ is the product of the probabilities for the individual tracks.

$$P(n_1 \ldots n_m, 0|m) = P_o(n_1) \ldots P_o(n_m)$$

These probabilities are the initial conditions for the system of differential equations.

Probability of Survival

$P(0 \ldots 0, t|m)$ is the probability that the nucleus has reached the survival state $n_1 = 0 \ldots n_m = 0$, $x = 0$ at time t, given that there are m tracks. Let $P_s(t)$ be the probability that the nucleus has reached a survival state at time t, averaged over all possibilities for the number of tracks. Since $P_p(m;W)$ is the probability that there are m tracks, this average is:

$$P_s(t) = \sum_{m=0}^{\infty} P_p(m;W)\ P(0 \ldots 0, t|m) \quad .$$

Finally, let S denote the probability that the nucleus ultimately will reach a survival state, given a time interval sufficiently long so that the repair process has been completed; then $S = P_s(\infty)$.

These are all of the elements of the Markov problem. $P_p(m;W)$, the distribution for the number of tracks, is a known function of the dose. $P_o(k_i)$, the distribution for the initial number of lesions along a track, is related to the average number of lesions per unit length of track and the shape and dimensions of the nucleus. Given $P_o(k_i)$, the differential equations for $P(n_1 \ldots n_m, t|m)$ could, in principle, be solved as a function of the three transition rate parameters; λ, κ, and μ. Finally, the average of $P(0 \ldots 0, \infty|m)$ over m completes the calculation for the probability of ultimate survival S as a function of dose and the various parameters.

III. MARKOV MODEL FOR THE CASE OF X RAYS

In the case of X rays the lesions are not located along a track; they are distributed randomly throughout the nucleus. This simplifies both the notation and the basic system of differential equations.

Let k denote the initial number of lesions in a particular nucleus, and let U denote the average number of lesions for all nuclei. Then U is proportional to the dose of radiation and k has a Poisson distribution with mean U:

$$P_p(k;U) = \frac{1}{k!} (U)^k e^{-U}$$

The initial state of the nucleus is described simply by the number k.

Let N denote the number of unrepaired lesions remaining in the nucleus at time t, and let x denote the number of misrepairs that have occurred. The state of the nucleus at time t is described by N,x. A self-repair is a transition between the states:

$$(N,x) \rightarrow (N-1,x')$$

and a cross repair is a transition between the states:

$$(N,x) \rightarrow (N-2,x').$$

Since there is no track structure, there is only one transition rate for cross repair, which shall be denoted by κ. The total transition rates for self-repair and cross-repair are: λN and $\kappa N(N-1)$, respectively.

Let P(N,t) denote the probability that at time t the nucleus is in the state N,x with x = 0. Then P(N,t) satisfies the system of equations:

$$\dot{P}(N, t) = \phi\lambda(N+1)\, P(N+1, t)$$

$$+ \delta\kappa(N+2)(N+1)\, P(N+2, t)$$

$$- [\lambda N + \kappa N(N-1)]\, P(N,t)$$

The initial conditions for this system are:

$$P(N, 0) = P_p\ (N;U)$$

where $P_p(N;U)$ is the Poisson distribution with mean U. The probability that the nucleus has reached the survival state at time t is:

$$P_s(t) = P(0,t)$$

and the probability of ultimate survival is $S = P_s(\infty)$.

IV. SOLUTIONS OF THE MARKOV MODEL

The differential equations of the Markov model simplify for the case that all quadratic repair is misrepair, $\delta = 0$. All the solutions in this section are for that case. These solutions are: (1) an exact solution for the case of X rays, (2) an exact solution for the case of ionizing particles with $\mu = \kappa$, (3) an exact solution for the case of ionizing particles with $\mu = 0$, and (4) an approximate solution for the case of ionizing particles with arbitrary values of μ.

Solution 1. X Rays

The differential equation for the case of X rays with $\delta = 0$ is:

$$\dot{P}(N,t) = \phi\lambda(N+1)\, P(N+1,t) - [\lambda N + \kappa N(N-1)]\, P(N,t)$$

and the initial conditions are:

$$P(N,0) = P_p(N;U) \quad .$$

Because the differential equation is linear in P, the sum of two or more solutions is also a solution. Consequently, the solution of the differential equation for the actual initial conditions can be written as a sum of solutions, each of which has a simpler initial condition.

Let $P(N,t|k,0)$ satisfy the differential equation with the simple initial condition that at $t = 0$ the probability is one that the nucleus has exactly k lesions, that is,

$$P(N,0|k,0) = \delta_{Nk}$$

where δ_{Nk} is the Kronecker delta, which equals one for N = k and zero otherwise. Then the sum of these solutions given by:

$$P(N,t) = \sum_{k=0}^{\infty} P(N,t|k,0)\ P(k,0)$$

satisfies the differential equation with the initial conditions P(N,0), which are the actual initial conditions of the Markov model. P(N,t) constructed in this way is the desired solution of that model.

The coupled system of differential equations can be solved for the simple initial conditions because the probability of states with more than k lesions remains zero for all time. The equation for P(k,t|k,0) is solved first because the only probability that is coupled to it, P(k+1,t|k,0), is a known quantity, namely zero. Once the solution for P(k,t|k,0) is known, the equation for P(k-1,t|k,0) can be solved, and from that solution, the equation for P(k-2,t|k,0) can be solved, and so on until finally the equation for P(0,t|k,0) is solved.

Because the coefficients in the differential equation are constants, the solution P(N,t|k,0) is a sum of exponentials in time:

$$P(N,t|k,0) = \sum_{J=0}^{k-N} A^{j}_{k,N}\ \ e^{-\alpha_{k-j}t}$$

where the exponents are:

$$\alpha_N = \lambda N + \kappa N(N-1)$$

and

$$A^{j}_{k,N} = \frac{(\phi\lambda)^{k-N}\ (N+1)(N+2)\ \ldots\ (k-1)k}{(\alpha_N-\alpha_{k-j})\ \ldots\ (\alpha_{k-1}-\alpha_{k-j})(\alpha_k-\alpha_{k-j})}$$

and the factor $(\alpha_{k-j}-\alpha_{k-j})$ is excluded from the denominator.

The probability of ultimate survival is related to the value of P(N,t k,0) for N = 0 and t = ∞. The above formulas give this quantity as:

$$P(0,\infty|k,0) = A^{k}_{k,0}$$

$$= \frac{\phi^k\lambda^k\ 1\cdot 2\ \ldots\ k}{\alpha_1\ \cdot\ \alpha_2\ \ldots\ \alpha_k}$$

$$= \frac{\phi^k\ \lambda^k\ 1\cdot 2\ \ldots\ k}{\lambda(2\lambda\ +\ 2\kappa)\ \ldots\ (\lambda k\ +\ \kappa k\ (k\ -\ 1))}$$

$$= \frac{\phi^k\ \varepsilon^k}{\varepsilon\ (\varepsilon\ +\ 1)\ \ldots\ (\varepsilon\ +\ k\ -\ 1)}$$

where ε is defined to be λ/κ.

The probability of ultimate survival is the value of P(N,t) for N = 0 and t = ∞, which is a weighted sum of the $P(0,\infty|k,0)$:

$$P(0,\infty) = \sum_{k=0} P(0,\infty|k,0)\ P(k,0)$$

Sums that are similar to this one will occur for the other cases, so it is convenient to define a function Z that includes all these sums. We define:

$$Z(\phi,\varepsilon,U) = \sum_{k=0} \frac{1}{k!}\ U^k\ e^{-U}\left[\frac{\phi^k\ \varepsilon^k}{\varepsilon(\varepsilon\ +\ 1)\ \ldots\ (\varepsilon\ +\ k\ -\ 1)}\right]$$

The probability of ultimate survival is:

$$S = P(0,\infty) = Z(\phi,\varepsilon,U)$$

for the case of X rays.

Solution 2. Ionizing Particles with $\mu = \kappa$

The differential equation for the case of ionizing particles with $\delta = 0$ is:

$$\dot{P}(n_1 \ldots n_m, t|m) = \phi\lambda \sum_i (n_i+1)\, P(n_1 \ldots n_i+1 \ldots n_m, t|m)$$

$$-\left[(\lambda-\kappa) \sum_i n_i + (\kappa-\mu)\sum_i n_i^2 + \mu \sum_i n_i \sum_j n_j\right) P(n_1 \ldots n_m, t|m)\Bigg] .$$

For $\mu = \kappa$ the $\sum_i n_i^2$ term drops out of the equation. The remaining terms can be written as functions of the total number of lesions on all m tracks, $N = \sum_i n_i$. Define $P(N, t|m)$ as the sum of the probabilities for all states that have N total lesions:

$$P(N, t|m) = \sum_{n_1 \cdots n_m}^{*} P(n_1 \ldots n_m, t|m)$$

where * means that the sum is restricted to those combinations of $n_1 \ldots n_m$ for which $\sum_i n_i = N$.

The initial conditions on $P(N, t|m)$ are:

$$P(N,0|m) = \sum_{n_1 \cdots n_m}^{*} P_0(n_1) \ldots P_0(n_m) \quad .$$

If the initial distribution on each track, $P_0(k_i)$, is Poisson with mean V, then the distribution for the total number of initial lesions, $P(N, 0|m)$, also will be Poisson with mean mV:

$$P(N,\ 0|m) = \frac{1}{N!}\ (mV)^N\ e^{-mV}$$

The differential equation for $P(N,\ t|m)$ is obtained by summing terms in the differential equation for $P(n_1 \ldots n_m,\ t|m)$. The result is:

$$\dot{P}(N,\ t|m) = \phi\lambda(N+1)\ P(N+1,\ t|m) - [\lambda N + \kappa N(N-1)]P(N,\ t|m)$$

This equation is identical to that for X rays. In order to pursue this point, average $P(N,t|m)$ over the number of tracks. Define $P(N,t)$ by:

$$P(N,t) = \sum_{m=0}^{\infty} P(N,t|m)\ P_p(m;W) \quad .$$

Then $P(N,t)$ also satisfies the differential equation for X rays. However, the solutions for ionzing particles and for X rays are different because the initial conditions are different. For ionizing particles the initial distribution is:

$$P(N,0) = \sum_{m=0}^{\infty} P(N,0|m)\ P_p(m;W)$$

which is not a Poisson distribution even though each $P(N,0|m)$ is a Poisson distribution. $P(N,0)$ for ionizing particles has mean WV and variance $WV + WV^2$. This is larger than the variance of a Poisson distribution by WV^2. The reason is that ionizing particles tend to produce lesions in bunches, V lesions on the average for each particle passing through the nucleus, rather than one at a time as in the case of X rays.

However, the solution for X rays is a limiting case of that for ionizing particles with $\mu = \kappa$. The solution for X rays is the limit as $V \to 0$ and $W \to \infty$

such that the product WV remains fixed, WV = U. When V → 0, the ratio of the probability of more than one lesion per track divided by the probability of exactly one lesion per track goes to zero, so lesions do not tend to occur in bunches.

For the general case of finite V, the initial distribution for P(N,t) is a complicated function, so it is more convenient to calculate P(N,t|m), whose initial distribution is Poisson, and then average this over m to get P(N,t). The method of solution exactly follows the case of X rays. P(N,t|m) is written as a sum of solutions that have the simple initial conditions:

$$P(N,t|m) = \sum_{k=0}^{\infty} P(N,t|k,0)\ P(k,0|m)$$

where P(N,t|k,0) is the solution for the case of X rays. The probability of ultimate survival given that there are m tracks is:

$$P(0,\infty|m) = \sum_{k=0}^{\infty} P(0,\infty|k,0)\ P(k,0|m) = Z(\phi,\varepsilon,mV)$$

since P(k,0|m) is a Poisson distribution with mean mV. Finally, the probability of ultimate survival, averaged over the number of tracks is:

$$S = \sum_{m=0}^{\infty} P(0,\infty|m)\ P_p(m;W) = \sum_{m=0}^{\infty} \frac{1}{m!}\, W^m\, e^{-W}\, Z(\phi,\varepsilon,mV)$$

for the case of ionizing particles with $\mu = \kappa$.

Solution 3. Ionizing Particles with $\mu = 0$

For $\mu = 0$ the between-track cross-repair term drops out of the differential equation. Initially there is no correlation between n_i and n_j. For $\mu = 0$

there is no coupling between them in the differential equation, therefore they remain uncorrelated for all time. Thus, $P(n_1 \ldots n_m, t|m)$ factors:

$$P(n_1 \ldots n_m, t|m) = P(n_1,t) \ldots P(n_m, t)$$

As a result, the differential equation separates into m identical equations. Since there is no difference between any of the tracks, the subscripts will be dropped and n will denote the number of lesions on any one of them. The differential equation for P(n,t) is:

$$\dot{P}(n,t) = \phi\lambda(n+1)\, P(n+1,t) - [\lambda n + \kappa n(n-1)]\, P(n,t)$$

This is the same as the equation for X rays. The initial condition for this case is that P(n,0) is a Poisson distribution with mean V:

$$P(n,0) = P_p(n;V)$$

The method of solution again follows the case of X rays. P(n,t) is written as:

$$P(n,t) = \sum_{k=0}^{\infty} P(n,t|k,0)\, P(n,0)$$

where $P(n, t|k, 0)$ is the solution for the case of X rays. Consequently,

$$P(0,\infty) = \sum_{k=0}^{\infty} P(0,\infty|k,0)\, P(n,0) = Z(\phi,\varepsilon,V)$$

This is the probability that one track ultimately evolves to the state of total eurepair. The probability of ultimate survival given that there are m tracks is the probability that m independent tracks reach this state, namely $P(n_1 \ldots n_m, t|m)$ for $n_1 = 0, \ldots n_m = 0$, and $t = \infty$. This is

$$P(0\ldots0,\infty|m) = P(0,\infty)\ \ldots\ P(0,\infty) = [Z(\phi,\epsilon,V)]^m$$

Finally, the probability of ultimate survival, averaged over the number of tracks is:

$$S = \sum_{m=0} P(0\ \ldots\ 0,\infty|m)\ P_p(m;W) = \sum_{m=0}^{\infty} \frac{1}{m!}\ W^m\ e^{-W}\ Z^m = e^{-[1-Z(\phi,\epsilon,V)]W}$$

The final sum was possible in closed form because for this case Z is not a function of m. The formula for S shows that it has a purely exponential dependence on the mean number of tracks per nucleus, W, and hence a purely exponential dependence on the dose of radiation for the case of ionizing particles with $\mu = 0$, that is, when between-track cross-repair is negligible.

Solution 4. Ionizing Particles with Arbitrary μ

The value of Solutions (2) and (3) is that the solutions for those cases bound the solution for arbitrary values of μ in the range $0 \leq \mu < \kappa$.

For arbitrary μ an approximate solution similar to solution (2) can be obtained by approximating the $\sum_i n_i^2$ term in the differential equation for $P(n_1\ \ldots\ n_m,t|m)$ by a function of N. This function must be chosen so that the cross-repair terms are zero for $N = 1$. It can be shown that, if each n_i had a Poisson distribution (which initially it does), then the average value of $\sum_i n_i^2$ for those combinations of $n_1 \ldots n_m$ for which $\sum_i n_i = N$ is:

$$E\left[\sum_{i=1}^{m} n_i^2\right] = N + N(N-1)/m \quad .$$

If this average value is used for the $\sum_i n_i^2$ term, then all terms in the differential equation for $P(n_1\ \ldots\ n_m,t|m)$ are functions of N and not the individual n_i. Consequently, an equation an be found for $P(N,t|m)$ as in Solution (2). The result is:

$$\dot{P}(N,t|m) = \phi\lambda(N+1)\ P(N+1,t|m) - [\lambda N + (\mu + (\kappa-\mu)/m)N(N-1)]\ P(N,t|m)]$$

The initial conditions are the same as in Solution (2):

$$P(N,0|m) = P_p(N;mV)$$

a Poisson distribution with mean mV. The solution is found by the same method:

$$P(N,t|m) = \sum_{k=0}^{\infty} P(N,t|k,0)\ P(k,0|m)$$

However, for this case

$$P(0,\infty|k,0) = \frac{\phi^k\ \gamma^k}{\gamma(\gamma+1)\ \ldots\ (\gamma+k-1)}$$

where

$$\gamma = \frac{\lambda}{\mu + (\kappa-\mu)/m} = \frac{m\varepsilon}{m\theta + 1 - \theta}$$

because the cross-repair term has a different coefficient than in Solution (2). The probability of ultimate survival, given that there are m tracks is:

$$P(0,\infty|m) = \sum_{K=0}^{\infty} P(0,\infty|k,0)\ P(k,0|m) = Z(\phi,\gamma,mV)$$

Finally, the probability of ultimate survival, averaged over the number of tracks is:

$$S = \sum_{m=0}^{\infty} P(0,\infty|m)\ P_p(m;W) = \sum_{m=0}^{\infty} \frac{1}{m!}\ W^m\ e^{-W}\ Z(\phi,\gamma,mV)$$

for the case of ionizing particles with arbitrary values of μ in the range $0 \leq \mu \leq \kappa$. For $\mu = \kappa$ this formula reduces to that for Solution (2).

Summary of Solutions

1. For X rays the probability of ultimate survival, S, is:

$$S = Z(\phi,\varepsilon,U).$$

2. For ionizing particles with $\mu = \kappa$:

$$S = \sum_m P_p(m;W)\ Z(\phi,\varepsilon,mV)$$

3. For ionizing particles with $\mu = 0$:

$$S = e^{-[1-Z(\phi,\varepsilon,V)]W}$$

4. For ionizing particles with arbitrary μ, approximately:

$$S = \sum_m P_p(m;W)\ Z(\phi,\gamma,mV)$$

where $P_p(m;W)$ is the Poisson distribution with mean W.

V. PROPERTIES OF THE SOLUTIONS

Limiting Cases

The expressions for the probability of ultimate survival, S, reduce to simple forms for various limiting cases. Some of these limiting cases involve extreme values of parameters, which would not be expected to describe an actual cell, however, they are useful as bounds on the possible range of values for S. In each case these limiting expressons agree with direct calculations of the probability of ultimate survival, thereby providing checks on the solutions (1) through (4) of Section IV.

$\phi = 0$. For this case the probability of ultimate survival for the case of X rays reduces to:

$$S = Z(o,\varepsilon,U) = e^{-U}$$

which is independent of ε. For ionizing particles S reduces to:

$$S = \sum_m \frac{1}{m!} W^m e^{-W} e^{-mV} = e^{-(1-a)W}$$

where $a = e^{-V}$, and is independent of both ε and θ. Solutions (2), (3), and (4) of Section IV each reduce to this expression.

These limiting expressions can be explained as follows. Linear repair occurs for $\phi = o$, but none of it is eurepair. Therefore, for the case of X rays, the probability of ultimate survival equals the probability that initially a particular nucleus had no lesions, given that the average number of lesions per nucleus is U. This probability is e^{-U}, so the expression for $Z(\phi,\varepsilon,U)$ reduces to the correct value in this limit.

For the case of ionizing particles with $\phi = 0$, the probability of ultimate survival equals the probability that initially each track of a particular nucleus had no lesions, given that for the nuclei as a whole the average number of lesion per track is V and the average number of tracks per nucleus is W. The probability that a particular track initially had no lesions is e^{-V}, and the same probability for m independent tracks is e^{-mV}. The probability that a nucleus has exactly m tracks through it is $W^m e^{-W}/m!$. The probability that a particular nucleus initially had no lesions is the product of these two factors summed over all values for m, which is precisely the expression for S given above for this case.

The expressions for S do not simplify for $\phi = 1$.

It can be shown that $\partial Z/\partial\phi > 0$ and $\partial S/\partial\phi > 0$. Consequently, the values of S corresponding to any increasing sequence of values of ϕ, and to fixed values of the other parameters, is an increasing sequence, that is, for

$$0 < \phi_1 < \phi_2 \ldots < 1,$$

$$S(0) < S(\phi_1) < S(\phi_2) \ldots < S(1).$$

<u>$0 < \varepsilon << 1$</u>. For this case the probability of ultimate survival for the case of of X rays, given by Solution (1) of Section IV, reduces to:

$$S = Z(\phi,0,U) = (1 + \phi U)e^{-U},$$

and that for ionizing particles with $\mu = 0$, given by Solution (3), reduces to:

$$S = \sum_m \frac{1}{m!} W^m e^{-W} (1+\phi V)^m e^{-mV} = e^{-(1-b)W} \quad ,$$

where

$$b = (1+\phi V)e^{-V} \quad ,$$

and that for ionizing particles with $\mu \neq 0$, given by Solutions (2) and (4), reduces to:

$$S = \sum_m \frac{1}{m!} W^m e^{-W}(1+m\phi V)\ e^{-mV} = (1+\phi VWe^{-V})\ e^{-(1-a)W} \quad ,$$

where again a is e^{-V}.

In order to understand these limiting expressions consider first the case of X rays with $\varepsilon << 1$. The probability of ultimate survival equals the probability that initially a nucleus had no lesions, plus the probability that it had one lesion that was eurepaired, plus the probability that it had two lesions that were eurepaired, plus etc. For $\varepsilon << 1$ the probability that two lesions will linear repair is negligible compared to the probability that they will cross repair, since $\lambda << \kappa$. However, one lesion by itself can not cross repair; it must eventually either linearly eurepair with probability ϕ or linearly misrepair with probability $(1-\phi)$, although for $\lambda << \kappa$ this linear repair will occur much more slowly than cross-repair in other nuclei that have two or more lesions. The probability that initially a nucleus had no lesions is e^{-U}, and the probability that it had one lesion that was eurepaired is ϕUe^{-U}, therefore, for $\varepsilon << 1$, S is the sum of these two terms, which is the expression given above for this case.

If ϵ were exactly zero, then linear repair would never occur and S would equal e^{-U}. However, this exceptional case does not give a useful bound for the solutions of Section IV, so it will not be considered further.

For the case of ionizing particles with $\mu = 0$ and $\epsilon << 1$, the quantity b is the probability that a track initially had no lesions or had one lesion that was eurepaired. Then b^m is the same probbility for m independent tracks, and the expression for S given above is b^m averaged over all possible values for m.

The case of ionizing particles with $\mu \neq 0$ differs from the last case in that between-track cross repair will very likely occur instead of linear repair, if two tracks in a nucleus each have one lesion.

$\underline{\epsilon = \infty}$. For this case the probability of ultimate survival for X rays reduces to:

$$S = Z(\phi,\infty,U) = \sum_k \frac{1}{k!} \phi^k U^k e^{-U} = e^{-(1-\phi)U} \quad ,$$

and those for ionizing particles, Solutions (2), (3), and (4) each reduce to:

$$S = \sum_m \frac{1}{m!} W^m e^{-m} \; e^{-(1-\theta)mV} = e^{-(1-c)W}$$

where

$$c = e^{-(1-\phi)V} \quad ,$$

which is independent of θ.

For $\epsilon = \infty$ there is no quadratic repair. For the case of X rays, the probability that initially a nucleus had exactly k lesions is $U^k \; e^{-U}/k!$, and the probability that all k of them ultimately were eurepaired is ϕ^k. The

probability that all the lesions in the nucleus were eurepaired is the product of these two factors summed over all values for k, which is the expression for S given above for this case.

For the case of ionizing particles with $\epsilon = \infty$, the quantity c is the probability that all the lesions on one track were eurepaired, and c^m is the same probability for m tracks. The probability that all the lesions in the nucleus were eurepaired is c^m averaged over all values for m, which is the expression for S given above for this case.

It can be shown that $\partial Z/\partial \epsilon \geq 0$ and $\partial S/\partial \epsilon \geq 0$, and that they equal zero only for certain limiting cases. Consequently, the values of S corresponding to any increasing sequence of values of ϵ, and to fixed values of the other parameters, is an increasing sequence, that is, for $0 < \epsilon_0 \ll 1$, and for $\epsilon_0 < \epsilon_1 < \epsilon_2 \ldots < \infty$,

$$S(\epsilon_0) < S(\epsilon_1) < S(\epsilon_2) \ldots < S(\infty).$$

This ordering is shown in Figures 1 and 2, which display the graphs of S vs. U for the case of X rays with $\phi = 1.0$ and 0.5. Note that for each value of U the range of values for S decreases as ϕ decreases.

$\mu = 0$ and $\mu = \kappa$. The expressions for these limiting cases for ionizing particles are the exact Solutions (3) for $\theta = 0$ and (2) for $\theta = 1$. It can be shown that $\partial S/\partial \theta \leq 0$, and equals zero only for certain limiting cases. Consequently, the values of S corresponding to any increasing sequence of values of θ, and to fixed values of the other parameters, is a decreasing sequence, that is, for $0 < \theta_1 < \theta_2 \ldots < 1$,

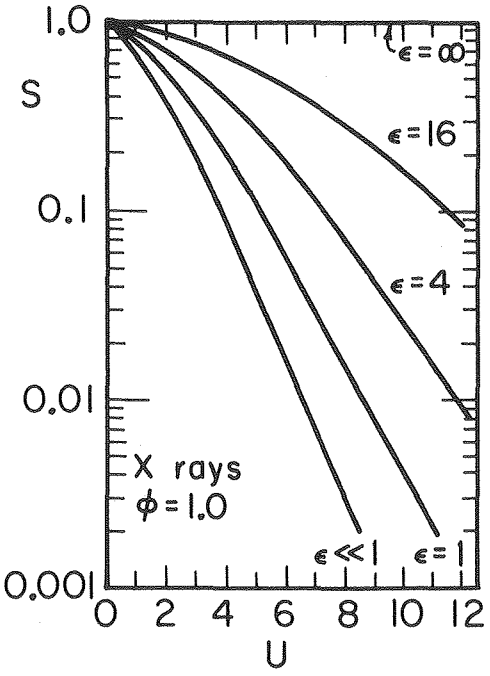


Fig. 1

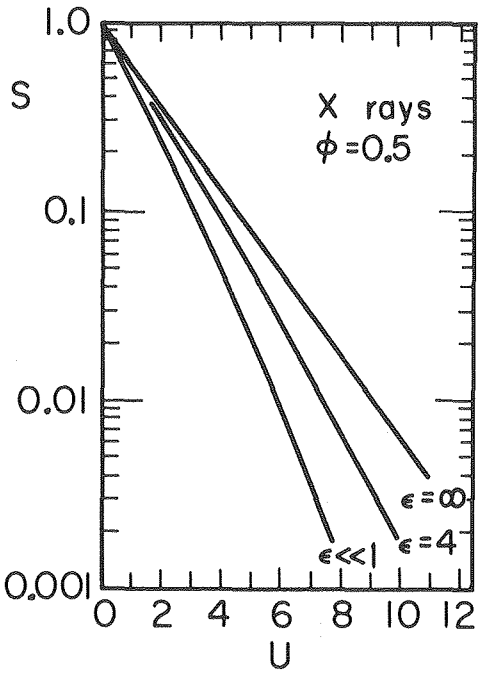


Fig. 2

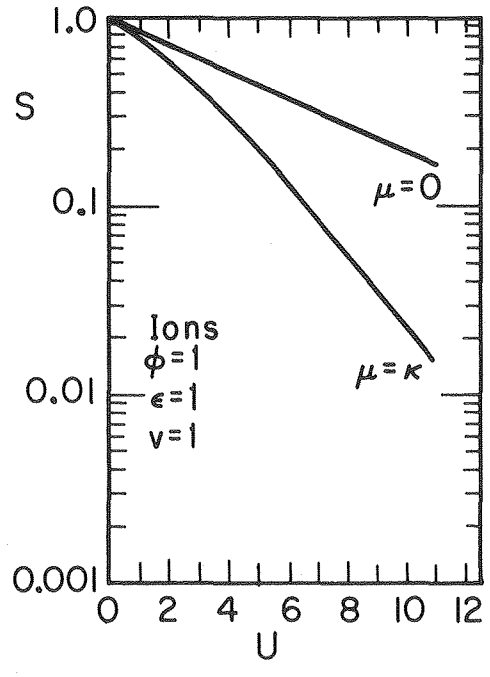


Fig. 3

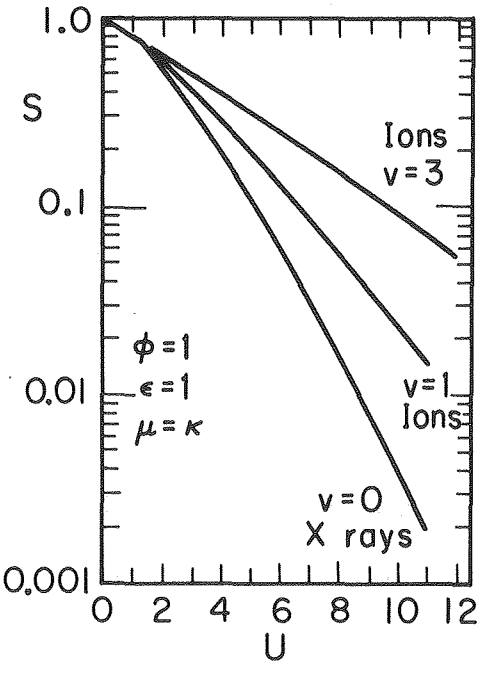


Fig. 4

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$$S(1) < \ldots < S(\theta_2) < S(\theta_1) < S(0) \quad .$$

Solutions (2) and (3) are shown in Figure 3, which displays the graphs of S vs. U for the case $\phi = 1$, $\epsilon = 1$, and $V = 1$, where U is the average number of initial lesions per nucleus, $U = VW$.

The approximate Solution (4) equals Solution (2) for $\theta = 1$, however, for $\theta = 0$ the approximate solution is less than Solution (3). Thus, for all θ in the range $0 \leq \theta \leq 1$, the approximate solutions also are bounded by the exact Solutions (2) and (3).

$\underline{0 < V < \infty}$. For the case of ionized particles the probability of ultimate survival for different values of V also are ordered, where V is the average number of initial lesions per track. One can show that $\partial Z/\partial V \leq 0$ and $\partial S/\partial V \leq 0$, and that they equal zero only for the limiting case $\epsilon = \infty$ and $\phi = 1$, that is for no misrepair. Consequently, the values of S corresponding to any increasing sequence of values of V, and to fixed values of the other parameters (specifically: ϕ, ϵ, θ, and W), is a decreasing sequence, that is, for $0 < V_1 < V_2 \ldots$,

$$S(0) > S(V_1) > S(V_2) \ldots \quad .$$

This ordering is as expected; with more lesions per track and the same number of tracks fewer cells survive.

Next consider the variation in S when V is varied and $U = VW$ is fixed, where U is the average number of initial lesions per nucleus. This shows the pure effect of the track structure on survival, that is, the effect of the same total number of lesions on the average, but distributed in larger or smaller bunches per track. For fixed U, $\partial S/\partial V$ can be positive or negative. In

general, $\partial S/\partial V < 0$ for U less than some critical value, U_{crit}, which is a function of ϕ, ε, θ, and V; and for $U > U_{crit}$ the inequality reverses: $\partial S/\partial V > 0$. Consequently, the ordering of the values of S for a sequence of values of V reverses; that is, in the region $U > U_{crit}$ the graphs of S vs. U for larger values of V (higher LET) lie above those for smaller values of V (lower LET). This order is shown in Figure 4, which displays the graphs of S vs. U for the case $\phi = 1$, $\varepsilon = 1$, and $\mu = \kappa$. The graph for $V = 0$ crosses that for $V = 1$ near $U = 1.5$. For fixed U more cells survive for larger V than for small V; one reason is that the probability that the nucleus has no tracks through it is $e^{-U/V}$, which is larger for larger V.

Finally, consider the variation in S when V is varied for fixed dose. Let A denote the area of the projection of the nucleus in the plane perpendicular to the particle beam, and let F denote the flux of radiation integrated over time and expressed as the number of particles per unit area. Then the average number of tracks through the nucleus, W, is:

$$W = AF.$$

Let D denote the radiation absorbed dose expressed as the energy absorbed per unit mass, let ρ denote the density of the absorbing material, and let LET denote the energy transfer per unit length; then

$$D = F\ LET/\rho.$$

Combining these two relations gives

$$W = \rho AD/LET,$$

and therefore,

$$U = \rho VAD/LET.$$

If V did not change with LET, then $\partial W/\partial V = 0$ and since $\partial Z/\partial V < 0$, it follows that $\partial S/\partial V$ would be negative for this case. On the other hand, if V was directly proportional to LET, fixed dose would be equivalent to fixed U, which gives a reverse ordering of survival curves for large U. Since experiments (Tobias et al., loc. cit.) show that survival decreases with increasing LET, this model of repair-misrepair implies that V must increase much less slowly with LET than in direct proportion. Assuming a particular functional dependence of V on LET, the graphs of survival vs. dose could be calculated and the model tested thereby. A numerical investigation of this will be pursued in a subsequent study.

LIST OF SYMBOLS

In the order they appeared in the text:

ϕ	fraction of linear repairs that are eurepairs
δ	fraction of quadratic repairs that are eurepairs
m	number of tracks through a particular nucleus
W	average value of m for all the nuclei
P_p	Poisson distribution
k_i	initial number of lesions along the i^{th} track through a particular nucleus
V	average value of k_i for all nuclei and tracks
n_i	number of unrepaired lesions remaining at time t on the i^{th} track
x	total number of misrepairs at time t in a particular nucleus
c_{jk}	transition rate from state j to state k of a nucleus
λ	transition rate for the self-repair of one lesion
κ^*	average transition rate for the cross-repair of one pair of lesions on the same track
μ^*	average transition rate for the cross-repair of one pair of lesions on one pair of tracks
κ	$\kappa^*/2$
μ	$\mu^*/2$
θ	μ/κ
$P(n_1,n_2,\ldots n_m,t\|m)$	probability at time t that a particular nucleus has $n_i \ldots n_m$ unrepaired lesions and no misrepaired lesions, given that there are m tracks through the nucleus

$P(0...0,t\|m)$	probability at time t that a particular nucleus has reached a survival state (no unrepaired or misrepaired lesions), given that there are m tracks through the nucleus
$P_S(t)$	probability at time t that a particular nucleus has reached a survival state, averaged over all possibilities for the number of tracks
$S = P_S(\infty)$	probability that a nucleus will ultimately reach a survival state
k	initial number of lesions in a particular nucleus
U	average value of k for all nuclei ($U = VW$ in the case of ionized particles)
N	number of unrepaired lesions remaining at time t in a particular nucleus ($N = \sum_i n_i$ in the case of ionized particles)
$Z(\phi,\varepsilon,U)$	function defined on page 13 (probability of ultimate survival in the case of X rays)
γ	ratio of linear and cross-repair coefficients defined on page 19
A	cross-sectional area of the nucleus
F	flux of radiation integrated over time
D	radiation absorbed dose

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